European Heart Journal Supplements (2025) **27** (Supplement 1), i56–i60
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae105

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Acute myocarditis: 2024 state of the art

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KEYWORDS
Myocarditis;
Immune checkpoint inhibitors;
Therapy;
Endomyocardial biopsy

Acute myocarditis (AM) is an inflammatory injury of the myocardium secondary to infections, systemic autoimmune disorders, medications, or toxic agents. The patient's genetic underground is a likely concurrent aetiology/contributory mechanism recently implicated in a proportion of AM. This review focuses on some critical new concepts of AM, updated indications for endomyocardial biopsy when cardiac magnetic resonance imaging is not sufficient or feasible, and estimation of long-term events after discharge. Furthermore, studies exploring AM as the cause of sudden cardiac death will be examined to assess the characteristics of patients who die due to AM before hospital admission. Managing the most severe clinical presentation, termed fulminant myocarditis (FM) characterized by haemodynamic instability due to ventricular arrhythmias or severe acute pump failure, will be summarized. Specific issues aimed to reduce the high mortality rate of FM, like early recognition, referring these patients from spoke centres to a hub centre, timely temporary mechanical circulatory support when indicated, early endomyocardial biopsy, and eventually immunosuppression, will be briefly discussed. Immune checkpoint inhibitors and desmosomal gene variant-associated AM will be highlighted as paradigmatic new forms of myocarditis.

Key concepts in acute myocarditis

Acute myocarditis (AM) is an inflammatory disease of the myocardium of sudden onset predominantly induced by viral infections but also associated with non-viral infections, systemic autoimmune disorders, and toxic agents and drugs.[1] Independently of the aetiology, immune dysregulation is responsible for myocardial injury, including in most cases of viral myocarditis, where viral exposure acts as a trigger.[2] Large administrative data sets suggest an incidence of 4–14 individuals per 100 000 yearly, mostly in men below 50 years of age.[1] Viral exposure, especially of respiratory viruses, is a major trigger for AM, with a prevalence that varies based on the methodological approach used to determine the viral aetiology. The search for respiratory viral genomes on nasopharyngeal swabs revealed that 18% had a positive result in a single-centre cohort of 50 patients.[3] Most of the patients had rhinoviruses, influenza viruses, and coronaviruses.[3] When the viral aetiology is estimated by the presence of viral prodromes such as fever, sore throat, and respiratory symptoms, it can range between 18 and 80% of patients with AM.[1,4] Systemic autoimmune diseases are associated with AM, with a prevalence of around 10% based on registries.[1,4,5] Among emerging causes of AM, there are the immune checkpoint inhibitors (ICIs), a family of new and effective anti-cancer agents associated with AM in 1% of patients treated with ICI.[1]

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Commonly used ICI agents are cytotoxic T lymphocyte antigen (CTLA4) inhibitors, such as ipilimumab, programmed cell death protein (PD-1) inhibitors, such as nivolumab and pembrolizumab, and the PD ligand 1 (PDL1) inhibitors, such as durvalumab. The combination of PD-1 or PDL1 with anti-CTLA4 increases the risk of AM, and especially anti-PD-1 inhibitors are associated with AM.[1] Immune checkpoint inhibitor-associated myocarditis often is associated with other immune-related adverse events, such as myositis and myasthenia-like syndromes, that can further raise the fatality risk of the disease, which ranges between 30 and 50%.[1]

Vaccine-associated AM is another entity that has been associated with smallpox, anthrax, and SARS-CoV-2 vaccines.[1] Anti-SARS-CoV-2 vaccines have been reported to be associated with the onset of AM, even if the incidence of AM was lower compared with AM associated with SARS-CoV-2 infection and with a favourable course in most cases.[1,6]

Genetic background has recently been recognized as a contributing factor in AM, and it can be identified between 8 and 16% of patients with AM, depending on the population where the genetic background is investigated.[7,8] Most patients with AM and a genetic background presenting with preserved left ventricular (LV) ejection fraction (EF) have desmosomal gene variants, in particular, *DSP* encoding for desmoplakin.[8] Most patients with AM and a genetic background presenting with persistently reduced LVEF or presenting with heart failure (HF) have sarcolemmal gene variants, especially *TTN* encoding for titin.[7]

Chest pain was the most common symptom at presentation in 82–95% of patients, followed by dyspnoea in 19–49%. Syncope, aborted sudden cardiac death (SCD), and cardiogenic shock are other uncommon presentations.[1] Mortality ranges from 1 to 7%, depending on the clinical presentation, aetiology of AM, and specific populations.[1] In 75% of patients, AM has an uncomplicated clinical presentation and a benign course with in-hospital mortality rates of ∼0% confirmed by several registries.[1,4] Conversely, in 25% of patients, AM displays a complicated clinical presentation (CCP) characterized by LVEF < 50% on the first echocardiogram, ventricular arrhythmias, or acute HF including fulminant presentation that carries in-hospital mortality or a need for heart transplantation (HTx) of 12%, and 15% at 5 years of follow-up.[4] Fulminant myocarditis (FM) presenting with cardiogenic shock at hospital admission or developing early after hospitalization (<48 h) occurs in 3–9% of patients with AM and represents the end of the spectrum of patients with CCP.[1,4,9] In patients with FM, the estimated in-hospital mortality or HTx at 60 days and 7 years after hospitalization is ∼28% and 48%, respectively.[9]

Sudden cardiac death and acute myocarditis

Acute myocarditis is also a recognized cause of SCD in the young population, with a prevalence of 6–10% in post-mortem examination studies (*Table 1*).[10–12] Sudden cardiac death can be caused by ventricular arrhythmias and, more rarely, by complete atrioventricular block. Ventricular arrhythmias can also be triggered by focal areas of myocarditis, which is the most common finding.[12] Alternatively, SCD can be caused by an abrupt pump failure due to massive inflammatory infiltrates causing a FM with extreme cardiogenic shock. The latter is a less common finding in patients with an out-of-hospital cardiac arrest. Data from the US National Registry on SCD in young competitive athletes report that over 32 years (1980–2011), 842 cases of SCD were documented, of which 57 (7%) were diagnosed as myocarditis. Among individuals who experience SCD due to AM, the mean age was 17 ± 5 years [46 were male (81%), and 11 were female (19%)]. Sarcoidosis was diagnosed in four individuals (0.5%) with a mean age of 26 ± 10 years, and all were male.[10] Another Italian study showed that among 273 young subjects below 35 years who experienced SCD between 1979 and 1998, 27 individuals (10%) had histopathologic evidence of myocarditis [mean age 21 ± 3 years, with 20 being male (74%)].[11] In 21 (78%) cases, death occurred at rest, including two cases of death during sleep. In six (22%) deaths occurred during physical effort, of whom three were competitive athletes.[11] Regarding prodromal symptoms, nine (33%) patients had a history of flu-like symptoms within 2 weeks before the event, two (7%) cases had a syncope before SCD, and only one (4%) reported chest pain. In all cases, histological examination showed a patchy interstitial inflammatory infiltrate.[11] Most cases (59%) showed a polymorphic infiltrate, nine cases (33%) had a lymphocytic infiltrate, and one case (4%) had a giant cell myocarditis (GCM).[11]

A large Danish study based on 14 294 young deaths from 2000 to 2009 showed that 1.363 (10%) were caused by SCD, of whom 753 (55%) underwent post-mortem examination.[12] In 42 cases (6%), the diagnosis was myocarditis.[12] The incidence of SCD myocarditis was estimated as 0.16 per 100 000 person-years.[12] Comparing patients with SCD due to myocarditis vs. patients with SCD due to other causes, those with myocarditis were younger at the time of death (31 vs. 34 years with non-myocarditis, $P = 0.027$) and had a trend for a higher proportion of associated infectious preceding death (7% vs. 3%, respectively, $P = 0.095$) with a proportion of influenza-related symptoms that was about three times higher in the weeks before death than in SCD from other causes.[12] The most common symptoms were indeed flu-like symptoms (29%), followed by chest pain (12%), syncope (7%), and dyspnoea (7%).[12] The authors also report that the incidence of SCD due to myocarditis was double in the male population than in the female. Overall, chest pain was the most common symptom reported in patients with AM admitted to hospital. In contrast, chest pain was rarely reported before SCD related to myocarditis, further supporting that in most cases, an arrhythmic event caused the death.

Endomyocardial biopsy and immunosuppression

Ideally, a definite diagnosis of myocarditis requires histologic evidence of myocardial inflammatory infiltrates or an increased number of T cells and macrophages associated with necrosis of nearby cardiomyocytes, based on the Dallas or the European Society of Cardiology criteria, excluding an ischaemic aetiology.[1] Anyway, the endomyocardial biopsy (EMB) is

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Table 1 Post-mortem examination series assessing the prevalence of myocarditis among young individuals with sudden cardiac death

First author	Years	Country	*N* autopsy	Age, male sex (%)	Type of population	Proportion of myocarditis	Among myocarditis, age, male sex (%)	Death at rest vs. during effort	Notes
Maron *et al.*[10]	1980–2011	USA	842	19 y 89% M	United States National Registry of Sudden Death in Athletes.	7% ($n = 57$) Sarcoidosis: 0.5% ($n = 4$)	17 y; 81% M Sarcoidosis: 26 y; 100% M	NA	In Whites 52%; in African American 42% Sarcoidosis: In African American 75%, in Whites 25%
Corrado *et al.*[11]	1979–1998	Italy	273	24 y 80% M	Veneto Region of Italy, prospective collection of sudden deaths ≤35 y.	10% ($n = 27$)	21 y; 74% M	At rest 21 (78%), of whom 2 during sleep. During effort in 6 (22%) of whom 3 competitive athletes.	Most frequent histology: polymorphous infiltrate (59%), lymphocytic (33%) and giant cell (4%).
Lynge *et al.*[12]	2000–2009	Denmark	753	NA	Nationwide study, deaths in people aged 1–49 y	6% ($n = 42$)	31 y; 69% M	At rest 38 (91%) of whom 18 during sleep. During activity 2 (5%). The remaining ones not specified	Post-mortem virology examination on myocardial tissue specimen performed in 10 (24%) with a positive result in 30% (2 cases of parvovirus B19 and one case with missing information on virus type)

M, male; *N*, numbers; NA, not available; y, years.

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an invasive procedure not available in all hospitals with a rate of complications estimated below 5%,[5] and for these reasons, generally <12% of all patients with suspected AM undergo an EMB and reach a definite diagnosis based on histology.[1,4] Even if EMB is the only tool that can characterize the inflammatory cells in the myocardium (i.e. eosinophilic myocarditis, GCM, lymphocytic myocarditis, or cardiac sarcoidosis), providing substantial diagnostic and prognostic information,[9] the sensitivity and clinical impact of EMB differ according to the presentation (for instance in patients with CCP vs. non-CCP) and the time from the onset of cardiac symptoms (performing EMB early vs. late after hospitalization).[1,5,13] The diagnostic yield of EMB is the highest when the clinical suspicion of AM is high, namely when there is a new onset of HF (within 2 weeks) with normal or mildly dilated LV and haemodynamic compromise, in case of HF associated with dilated cardiomyopathy of any duration related to allergic reaction or eosinophilia and in case of HF onset between 2 weeks and 3 months with LV dilation and ventricular arrhythmias or second- to third-degree atrioventricular block or failure to respond to usual HF therapies within 2 weeks of therapy.[1,13] The American Heart Association and American College of Cardiology associations propose these indications. In these cases, the sensibility of the EMB ranges from 21 to 39%, being capable of changing the course of the disease and modifying the therapeutic approach in ~25% of cases.[13] Other proposed clinical indications are in specific settings, such as AM associated with ICI therapies and AM or suspected chronic inflammatory cardiomyopathies with persistent/relapsing release of myocardial necrosis markers, primarily if associated with suspected/known autoimmune disorders or cardiac sarcoidosis.[1,13] Indication for EMB for patients with suspected AM associated with ICI relies on the relatively low sensitivity compared with other forms of AM of echocardiography due to preserved LVEF in almost half of the patients and cardiac magnetic resonance imaging (CMRI), which can reveal oedema in <50% of patients.

Cardiac magnetic resonance imaging is the primary diagnostic tool in almost all cases where the patients can tolerate the exam, especially in patients with a non-CCP. Endomyocardial biopsy could be proposed after CMRI for specific cases where the inflammatory pattern on CMRI could foresee specific aetiologies according to the likelihood of detecting a treatable disorder, for instance, cardiac sarcoidosis (*Figure 1*).[1]

Patients with severe forms, like those with FM who promptly undergo EMB (<48 h), seem to have a prognostic benefit compared with patients with FM who undergo EMB later, potentially because the findings derived by the EMB allow prompt identification of specific aetiologies potentially supporting the use of immunosuppressant agents.[6] Specifically, GCM has a worse outcome compared with eosinophilic myocarditis and lymphocytic myocarditis,[9] and patients with GCM generally require combined immunosuppressive therapies.[1,2] Patients with FM with GCM have a high rate of early death or HTx of up to 62.5% at 60 days, while patients with FM and eosinophilic myocarditis or lymphocytic myocarditis reported a cardiac death and HTx of 26.3% and 21.0% at 60 days, respectively.[9]

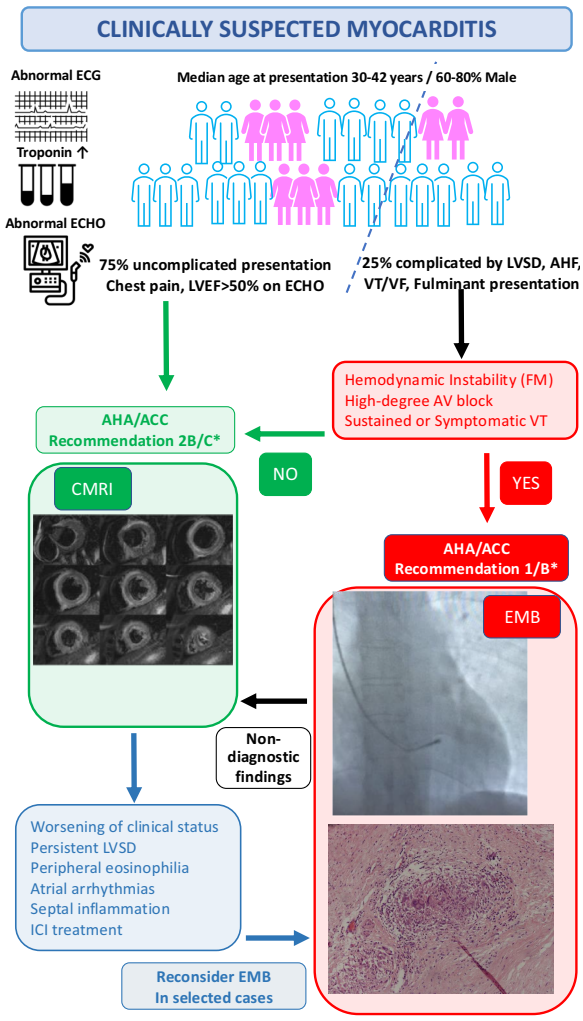

Figure 1 Indications for endomyocardial biopsy or cardiac magnetic resonance imaging (adapted from Ammirati *et al.*[1]) *Level of recommendation based on the American College of Cardiology and American Heart Association scientific statements. ACC, American College of Cardiology; AHA, American Heart Association; AHF, acute heart failure; AV, atrioventricular; CMRI, cardiac magnetic resonance imaging; ECHO, echocardiogram; EMB, endomyocardial biopsy; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Specific immunosuppressive therapies, mainly involving the administration of pulsed doses of methylprednisolone, could reduce myocardial inflammation, positively affecting the prognosis, even if data are still limited.[2] Expert consensuses recommend immunosuppression in specific aetiologies that can advantage most, like eosinophilic myocarditis, GCM, cardiac sarcoidosis, AM associated with ICI, and in the setting of systemic autoimmune disorders.[1,2] An international randomized controlled trial, the Myocarditis Therapy with Steroids (MYTHS, NCT05150704) trial, is currently assessing the efficacy and safety of early treatment with high doses of methylprednisolone in patients with severe lymphocytic AM, including those with FM.[2] This trial could provide evidence of the routine use of corticosteroids in patients with lymphocytic myocarditis presenting with acute HF or cardiogenic shock.

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Beyond immunosuppression, improving survival in patients with FM relies on a bundle of care that can summarized in the acronym R^2ABC: *R*apid recognition of patients with severe AM, *R*eferring patients from spoke centres to tertiary hub centres capable of positioning temporary mechanical circulatory supports (t-MCS) and performing EMB in critical patients, *A*ggressive (timely) positioning of t-MCS, *B*iopsy performed within 48 h from admission, and *C*onsider corticosteroid administration in specific aetiologies.[14]

Follow-up of patients with acute myocarditis and cardiac events after discharge

Identifying reliable biomarkers associated with adverse outcomes following AM is essential for optimizing long-term follow-up monitoring. While most cardiac events occur during the initial hospitalization, a residual risk of ~1% for cardiac death or HTx persists in the 5 years after discharge.[4] Clinical presentation and CMRI-derived markers have emerged as robust prognostic tools for patient stratification after AM.[1,15] Specifically, a CCP, as previously described, during the acute phase showed significant long-term prognostic implications.[4] Likewise, CMRI parameters, such as the presence of septal late gadolinium enhancement (LGE), a marker of myocardial fibrosis, and reduced LVEF (<50%), are also good predictors of major cardiac events, including cardiac death, HTx, aborted SCD, sustained ventricular arrhythmias, and HF hospitalization. In a retrospective study including 248 patients with AM who underwent CMRI before discharge, 13 major cardiac events (5.2%) occurred after a median follow-up of 4.7 years.[15] Complicated clinical presentation was found to be the strongest prognostic marker during long-term follow-up after AM.[15] The combination of CCP and septal LGE on baseline CMRI identified all patients with an event in the follow-up, likely because it could also identify rare causes of AM that can present with preserved LVEF but can have an unfavourable genetic background, like pathogenic or likely pathogenic desmosomal gene variants that are commonly associated with septal localization of LGE.[7,15]

In conclusion, most events occur during the initial phase of AM, and prompt recognition of the condition and risk-based management of patients must be ensured to reduce mortality and HTx in a generally young and healthy population. Surviving the acute phase is usually associated with a good mid- to long-term prognosis. Patients without CCP and septal LGE involvement and LVEF > 50% on CMRI have an uneventful follow-up, allowing less strict monitoring of these patients.[15]

Funding

E.A. received a grant from the Italian Ministry of Health (GR-2019-12368506; principal investigator of the investigator-driven Myocarditis Therapy with Steroids (MYTHS trial) and a grant from Italian Ministry of Health and NextGenerationEU (PNRR-MAD-2022-12376225).

Conflict of interest: E.A. is a consultant for Lexeo and was a consultant for Kiniksa, AstraZeneca, and Cytokinetics.

Data availability

No new data were generated or analysed in support of this research.

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